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ORIGINAL ARTICLE

Ionic liquid promoted one pot approach for the synthesis of pyrido[1,2-c][1,3,5]thiadiazin-4-ones and thiazolo[3,2-c][1,3,5]thiadiazin-4-ones in water

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Room temperature

Abstract A novel three component one pot methodology for rapid access to pyrido[1,2-c][1,3,5]thiadiazin-4-ones and thiazolo[3,2-c][1,3,5]thiadiazin-4-ones has been developed. A task specific ionic liquid [bmIm]SCN has been used as thiocyanating reagent. The reaction provides high yields of the product and proceeds at ambient reaction conditions in water. The use of water as the reaction medium and easy recyclability of the ionic liquid used as a reagent as well as promoter of the reaction endows the reaction with green aspects.

1. Introduction

Multicomponent reactions prove to be one of the key tools for efficient and speedy assembly of structurally complex and highly functionalized 'drug like' heterocycles as they provide a robust and straightforward approach toward the assembly using easily available starting materials (Jie et al., 2011; Domling and Ugi, 2000; Orru and de Greef, 2003; Sunderhaus and Martin, 2009). However, with the present paradigm focusing on green chemistry, there is a constant need for the development of operationally simple MCR methodologies that can promise benefits for organic syntheses in terms of atom economy, high yields and health and environmental safety, in a high throughput fashion. Water has emerged as a very desirable reaction media for organic syntheses because of its non-toxic, and environmentally benign nature. Very impressive results have been obtained during the last decade by implementing aqueous media in organic synthesis, specifically in the acceleration of MCR (Li, 2005; Pirrung and Sarma, 2004; Zonouz et al., 2012). The application of MCRs in water is a very promising field in synthetic chemistry (Dandia et al., 2012; Rajarathinam and Vasuki, 2012; Ma et al., 2010).

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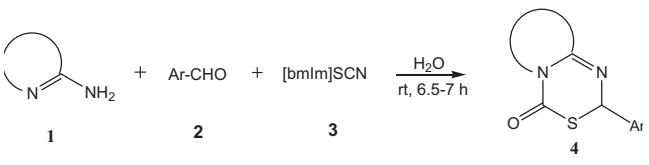
Room temperature ionic liquids have been attracting interest of synthetic community for a long period owing to their interesting properties like non-flammability, low vapor pressure, wide solvating ability and easy recyclability (Welton, 1999; Carlin and Wilkes, 1994).

The use of ionic liquids has broadened its scope from being only a reaction medium to performing its role as a catalyst and reagent (Wasserscheid and Keim, 2000; Brown et al., 2001; Leitner, 2003; Yang et al., 2003; Kumar and Pawar, 2004; Boon et al., 1986; Sheldon, 2001; Kim and Varma, 2005; Ranu and Jana, 2005; Zhu et al., 2005).

A novel task specific ionic liquid (TSIL) [bmIm]SCN (1-butyl-3-methylimidazolium thiocyanate) has been synthesized by Kamal and Chouhan (2005), which has proved excellent as a thiocyanating reagent. The use of metal thiocyanates, ammonium thiocyanate, trimethylsilyl isothiocyanate and many other reagents as thiocyanating reagents has been widely explored in the past. It has been observed that the low nucleophilicity of the SCN ion and poor stability of almost all the reagents used, render them rather unfit for use. Previous studies have also shown that the nucleophilicity of thiocyanate ion in [bmIm]SCN is much greater than that of KSCN in any ionic liquid (Kamal and Chouhan, 2005; Yadav et al., 2007; Gouda, 2013; Bacon and Guy, 1961; Pavlik et al., 1994; Nishiyama and Oba, 1987; Sasaki et al., 1981; Tamura et al., 1977; Burski et al., 1983; Iranpoor et al., 2000; Molina et al., 1982). The present protocol demonstrates the use of this ionic liquid as a reagent and a promoter of the reaction as well.

1,3,5-Thiadiazines and their derivatives are a significant class of biologically relevant heterocycles due to their anticancer (Temple et al., 1983), antimicrobial (Coburn et al., 1982; Chen et al., 1996), potential CNS (Malinka et al., 2002), antioxidant, antiprotozoal (Coro et al., 2011), and tuberculostatic (Zsolnai, 1968; Katiyar et al., 2003) properties. In addition, they are also used as herbicides (Chupp, 1973), insecticides (Nakaya et al., 1989) and miticides (Ikeda and Kanno, 1980). Pyridothiadiazine variants and thiazolothiadiazine variants particularly, have been reported in the literature to possess a wide range of biologically significant properties (Youssef et al., 2012; Neill et al., 1998; Dandia et al., 2004). One particular variant of pyridothiadiazine **PD 404182** has been known to show anti-HIV activity (Mizuhara et al., 2012). The established biological activities of these motifs combined with their interesting skeletal frameworks concur to classify them as intriguing synthetic exercises for organic chemists. Despite this fact, synthetic methodologies for their preparation have been very less explored till now.

In the light of the above mentioned facts and as a part of our ongoing work on the development of efficient methodologies to synthesize potentially bioactive heterocycles by eco-compatible methods (Siddiqui et al., 2003, 2010, 2012, 2013a–f), we herein report a novel and efficient strategy for the synthesis of potentially bioactive pyridothiadiazin-4-ones and thiazolothiadiazin-4-ones using 2-amino-heterocycles, aromatic aldehydes and [bmIm]SCN as starting materials. To the best of our knowledge, this is the first report on the use of TSIL [bmIm]SCN for heterocyclic synthesis. The reaction is promoted by ionic liquid and proceeds smoothly in water at room temperature to provide the target compounds in good to excellent yields (Scheme 1).



Scheme 1 Three component one-pot synthesis of pyrido[1,2-c][1,3,5]thiadiazin-4-ones and thiazolo[3,2-c][1,3,5]thiadiazin-4-ones.

2. Experimental

2.1. Methods and apparatus

The starting materials 2-aminopyridine, 2-aminothiazole, aromatic aldehydes, KSCN and ionic liquids [bmIm]Br and [bmIm]Cl are commercially available. The task specific ionic liquid [bmIm]SCN has been synthesized from ionic liquid [bmIm]OH according to a reported procedure (Yadav et al., 2007). Melting points were determined by the open glass capillary method (uncorrected). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II (400 MHz) FT spectrometer at 400 and 100 MHz, respectively, with $CDCl_3$ as solvent. Chemical shifts are reported in parts per million relative to TMS as internal reference. Mass (EI) spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analysis was performed on an Elementar vario EL.

2.2. General procedure for synthesis of pyrido[1,2-c][1,3,5] thiadiazin-4-ones and thiazolo[3,2-c][1,3,5]thiadiazin-4-ones **4**

A mixture of 2-aminopyridine/2-aminothiazole **1** (1.0 mmol), aromatic aldehyde **2** (1.0 mmol) and [bmim]SCN **3** (2.0 mmol), and 2 mL of distilled water was taken in a 50 mL round-bottomed flask and stirred at rt for 6.5–7 h. After completion of the reaction as indicated by TLC, the product was extracted with ether (3 × 25 mL). The combined extracts were evaporated under reduced pressure to leave the crude product, which was purified by column chromatography to afford pure target compound **4**.

***4a**: 2-phenylpyrido[1,2-c][1,3,5]thiadiazin-4(2H)-one:* White solid, mp-181–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 4.3 (s, 1H), 5.01 (d, 1H), 5.77 (m, 1H), 6.51 (m, 1H), 7.28 (d, 1H), 7.06–7.14 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 61.0, 111.7, 122.6, 125.8, 127.1, 127.8, 128.8, 133.0, 141.3, 164.2; MS: m/z = 242 $[M]^+$ Anal. Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.41; H, 4.20; N, 11.54.

***4b**: 2-(4-chlorophenyl)pyrido[1,2-c][1,3,5]thiadiazin-4(2H)-one:* White solid, mp-191–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 4.1 (s, 1H), 5.5 (d, 1H), 5.80 (m, 1H), 6.62 (m, 1H), 7.31 (d, 1H), 7.00–7.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 61.5, 111.9, 122.9, 126.0, 129.2, 129.7, 132.7, 133.1, 139.1, 164.3; MS: m/z = 278 $[M]^+$ Anal. Calcd for $C_{13}H_9ClN_2OS$: C, 56.42; H, 3.28; N, 10.12. Found: C, 56.40; H, 3.30; N, 10.13.

***4c**: 2-p-tolylpyrido[1,2-c][1,3,5]thiadiazin-4(2H)-one:* White solid, mp-185–187 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): δ = 2.35 (s, 3H), 3.91 (s, 1H), 5.2 (d, 1H), 5.67 (m, 1H), 6.51 (m, 1H), 7.28 (d, 1H), 6.94–7.03 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ = 24.3, 61.1, 111.5, 122.3, 125.5, 127.7, 128.7, 132.7, 136.6, 138.0, 159.2; MS:

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